IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Jane Hirsh, Whe-Yong Lo, and Kamal K. Midha

Serial No.: 09/858,016 Art Unit: 1616

Filed: May 15, 2001 Examiner: Gollamudi, Shirmila, S.

For: *PHARMACEUTICAL COMPOSITIONS FOR BOTH INTRAORAL AND ORAL ADMINISTRATION*

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Commissioner for Patents
P.O. Box 1450
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APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 33-57 in the Office Action mailed April 19, 2006, in the above-identified patent application. A Notice of Appeal was filed on July 19, 2006. An Advisory action was mailed on January 20, 2006.

The Commissioner is authorized to charge $310.00, the sum of fee for filing this Appeal Brief and a Petition for Extension of Time to extend the period for response for one month, to and including October 19, 2006 for a small entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Collegium Phamaceutical, the assignee of record.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 33-57 are pending and on appeal. Claims 1-32 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were amended in an amendment filed on December 22, 2005, in response to a final office action mailed on September 23, 2005. In the Advisory action mailed on January 20, 2006, the Examiner indicated that this amendment would not be entered. Appellants filed a Request for Continued Examination (RCE) on January 23, 2006, requesting entry of the amendment mailed December 22, 2005, and the Examiner acknowledged the RCE in the office action mailed on April 19, 2006. Claims 1-32 were cancelled and new claims 33-57 were added in the Amendment filed on June 13, 2003.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 33 defines a two component drug formulation. The first component is designed to rapidly release drug within the mouth, where it is taken up in an effective amount through the buccal or sublingual surface. Suitable drugs are low molecular weight compounds (typically under 350 daltons, see page 6, lines 13-15) or the specifically listed compounds (pages

9-10) that demonstrate rapid onset when administered intraorally (page 7, lines 20-23) since they are not ingested, but are absorbed directly into the systemic circulation from the mouth. These drugs may have a low bioavailability if administered orally due to first-pass metabolism (page 6, lines 15-19) as defined by claim 34. The second component is located within the first component and is designed to be released orally, where it is swallowed for uptake within the lower gastrointestinal tract. The intraoral portion is a film coating that is applied to the core or a compression coating that is compressed around the core (page 21, lines 22-24).

Dependent claims 36 and 37 define a composition wherein the unit dosage form is a tablet or multilayer tablet and the second oral portion is an inner core of the tablet surrounded by an outer coating (page 5, lines 12-22). The tablets may be coated with a film or a compression coating (page 21, lines 22-25) (claims 38 and 39).

Independent claim 41 defines a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient for uptake in the oral cavity in a therapeutically effective level, the active ingredient having a molecular weight not exceeding 350 daltons, or an active ingredient selected from the group consisting of the compounds listed on pages 9 and 10, a pharmaceutically acceptable effervescent agent which generates effervescence or a signaling system located between the first and second components, that is detectable by the patient (page 15, lines 5-25) and a second oral portion loaded within the first portion. The intraoral portion is a film coating applied to the core or a compression coating compressed around the core (page 21, lines 22-24). The release of the second component may be immediate, continuous, or released after a delay over a period of 0.5 to 12 hours (page 8, lines 1-4). The formulation may be chewable (page 8, line 5) (claim 47). The second oral component

may include a delayed release coating (page 24, lines 24-26) or a sustained release formulation (page 26, lines 24-26) releasing for 0.5 to 24 hours (page 27, line 1) (claims 43-46).

The dosage of the drug is low, in the range of 1 microgram to 50 mg, more typically 10 micrograms to 30 mg (page 6, lines 1-2) (claim 53). Claim 48 requires that the first intraoral component be released rapidly, in some cases within 10 minutes of contacting the saliva (page 20, lines 1-2).

Independent claim 55 defines a process for the preparation of a pharmaceutical composition in unit dosage, comprising two components with the limitations recited in claims 33, wherein the active ingredient exhibits first pass metabolism and has a molecular weight of less than 350 daltons as defined by claims 56 and 57.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

i) whether claims 33-57 are definite as required by 35 U.S.C. §112.

(ii) whether claims 33-39, 41-50, 51-56 are obvious under 35 U.S.C. 103(a) over GB 800,973 to Sterling ("Sterling") in view of U.S. Patent No. 6,140,319 to Powell et al. ("Powell") and further in view of DE 3338978 to Frömming ("Fromming") and U.S. Patent No. 3,898,323 to Fennell ("Fennell").

(iii) whether claims 41, 51, and 54 are obvious under 35 U.S.C. § 103(a) over Sterling, in view of Remington's Pharmaceutical Sciences, 18th Ed. (1990), page 844 ("Remington") and further in view of Fennell.

(iv) whether claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 and 49-57 are obvious under 35 U.S.C. 103(a) over U.S. Patent Publication No. 2001/0002999 by Neuser, et al. ("Neuser") in view of U.S. Patent No. 4,661,492 to Lewis et al. ("Lewis") and further in view of U.S. Patent No. 5,686,122 to Liedtke ("Liedtke").

(v) whether claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are obvious under 35 U.S.C. 103(a) over International Publication No. WO 00/35296 by Johnson ("Johnson").

(vi) whether claim 57 is obvious under 35 U.S.C. 103(a) over Johnson in view of U.S. Patent No. 5,310,561 to Jao, et al. ("Jao").

(vii) whether claims 33-43, and 49-57 are obvious under 35 U.S.C. 103(a) over U.S. Patent No. 5,053,032 to Barclay, et al. ("Barclay") in view of U.S. Patent No. 6,200,604 to Pather, et al. ("Pather").

(viii) whether claims 33-57 are obvious under the judicially created doctrine of obviousness-type double patenting, over claims 1-19 of U.S. Patent No. 6,863,901 and claims 1-20 of U.S. Application No. 11/041474.

(7) ARGUMENTS

(a) The Claimed Invention

Medications are typically administered in the prior art orally, intraorally, parenterally by injection, or intravenously, for release at a single site, immediately, continuously, or after a delay. Appellants have devised a method for administering one or more pharmaceutical agents in an effective amount, by both an intraoral and an oral means, in the same composition. The composition comprises two components. The first component is the intraoral component and the second component is the oral component, formulated such that it is formulated within the first component so that it is released after the first component, with the first component applied as a film coating or a compression coating around the second component. The pharmaceutical composition for intraoral administration must be capable of sublingual or buccal absorption. Not all drugs are capable of sublingual or buccal absorption. Most must either be low molecular weight (less than 350 daltons) or having a chemical composition The core includes a signaling

system such as flavor particles, color change, gas liberation etc., which is detected by the patient once the intraoral component is completely dissolve, such that the patient can swallow or chew and swallow the oral component. The advantage of this system is twofold treatment, in the case where the intraoral component is different from the oral component, such that concomitant administration can relieve different symptoms of the same disease, or in the case where both components have the same active ingredient, concomitant administration can work together to increase the total therapeutic effect of the individual pharmaceutically active ingredients.

(b) Rejection under 35 U.S.C. § 112

Claims 33-57 were rejected under 35 U.S.C. § 112, second paragraph, on the basis that the second oral portion is supposed to be released in the intestine and yet is capable of being chewed and swallowed. However, because the oral portion can be a delayed or sustained release formulation, and is swallowed, release will occur following passage through the stomach and in the intestine. Accordingly, even if the formulation is chewed and swallowed in the mouth, release occurs in the intestine. The Examiner also alleges that claims 1, 41, and 55 lack sufficient antecedent basis for the term "the core". Claim 1 has been canceled. It is assumed that the Examiner is referring to claim 33. Appellants will amend claims 33, 41, and 55 to define a core or to define the intraoral portion as a film coating or compression coating which is applied to the second oral portion, if necessary and solely to facilitate prosecution, however, it is believed it is clear and fully supported if one looks at the correct base claim. The Examiner also alleges that "comprises one or more of the outer layers" in claim 37 lack sufficient antecedent basis. This objection is unclear. Claim 37 depends from claim 35, which defines the composition of claim 33 in the form of a tablet or capsule unit dosage form. Claim 37 defines the tablet of claim 33 as a multilayer tablet, wherein the oral component comprises one or more

inner layers of the tablet and the intraoral component comprises one or more outer layers of the tablet. The antecedent basis is inherent in the claim itself.

(c) Rejections Under 35 U.S.C. § 103

Claims 33-39, 41-50, 51-56 were rejected as obvious over Sterling in view of Powell in further view of Fromming and further in view of Fennell. Claims 41, 51, and 54 were rejected as obvious Sterling in view of Remington and further in view of Fennel. Claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 and 49-57 were rejected as obvious over Neuser in view of Lewis and further in view of Liedtke. Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 were rejected as obvious over Johnson. Claim 57 was rejected as obvious over Johnson in view of Jao. Claims 33-43, and 49-57 were rejected as obvious Barclay in view of Panther.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

According to the MPEP 2143.01 "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000)".

Analysis

Claims 33-39, 41-50, and 51-56 are not obvious over Sterling in view Powell, and further in view of Frömming or Fennell. Claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are not obvious over Neuser in view of Lewis and further in view of Liedtke. Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious over Johnson.

Sterling

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, this having an outer medicinal layer soluble in the mouth. Sterling does not disclose a composition wherein an intraoral portion is a film coating or a compression coating. Sterling describes compositions wherein a drug is **dusted** onto a core of a second drug.

Powell

Powell describes the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris. There is no disclosure of intraoral and oral delivery, the need for two routes of delivery, or a means of achieving oral and intraoral delivery.

Frömming

Frömming describes the use of verapamil or gallopamil for sublingual or buccal administration administered in a tablet, a chewable capsule or a spray. One cannot tell if this is intraoral or oral, but it is certainly not both in a two component system where one is taught that an intraoral component should be released immediately.

Fennell

Fennell discloses a composition comprising miraculin and a non-toxic alkaline material. The composition can be powdered, liquid or formed into a tablet. In the coated tablet or

powdered form, the alkaline material can form a coating for the tablet. The coating can be applied by compression over the tablet core utilizing a tablet press of it is formed by tumbling the miraculin core in a drum containing alkaline material or into which the said alkaline material is sprayed.

Neuser

Neuser describes pharmaceutical compositions which can be administered orally and contain a fixed combination of at least one ***locally*** acting analgesic with a rapid onset of action and at least one ***systemically*** acting analgesic with a sustained action. The locally acting analgesic is not absorbed intraorally but is active at the surface it contacts.

Lewis

Lewis describes an analgesic composition in parenteral or sublingual unit dosage form comprising an active dose of buprenorphine and an amount of naltrexone sufficient to prove aversive to a narcotic addict by parenteral administration but insufficient to compromise the analgesic action of the buprenorphine.

Liedtke

Liedtke describes single dosage **topical** pharmaceutical formulations such as buprenorphine.

Barclay

Barclay describes an ***osmotic*** device for a delivering a drug into the mouth of a human patient (abstract). The device comprises a wall surrounding a compartment housing, a layer of an agent insoluble to very soluble in aqueous biological fluids such as saliva and a layer of fluid swellable hydrophilic polymer. A passageway in the wall connects the agent with the exterior of the device. The agent is released from the device by the combined actions of fluid being imbibed

through the wall into the compartment, producing a solution or suspension containing agent and by fluid being imbibed by the hydrophilic polymer causing it to expand and increase in volume, thereby exerting a force against the solution or suspension which is pushed through the passage way. Example 3 describes an osmotic device containing an overcoat of ibuprofen and HPMC. The overcoat layer is completely removed in 15-30 minutes. In some embodiments, the device can be used to extend the absorption of a drug that might be poorly absorbed throughout certain portions of the GI tract, by administering a predetermined percentage of the drug in the buccal cavity, followed by delivery of the remaining dose in the GI tract (Barclay, column 8, lines 28 to 35).

Pather

Pather describes a pharmaceutical dosage form comprising an orally administerable medicament in combination with an effervescent agent used as a penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa (col. 2, lines 7-11). Panther discloses that the effervescent agent can act to increase the rate and extent of absorption of the active agent by: (1) reducing the mucosal layer thickness and/or viscosity; (2) tight junction alteration; (3) inducing a change in the cell membrane structure; and (4) increasing the hydrophobic environment within the cellular membrane.

Johnson

Johnson describes a coated chewing gum, wherein the coating contains a medicament or active agent for systemic delivery upon chewing. The core of the chewing gum can also contain an active agent. There is no disclosure of an agent that is released and absorbed intraorally and an agent that is released and absorbed orally (i.e., in the lower gastrointestinal tract) – there is only disclosure of a composition that is released in the mouth and swallowed for absorption in

the lower gastrointestinal tract, as well as a second component that may also be swallowed intact for subsequent release and absorption in the gastrointestinal tract.

Claims 33-40, 42-46, and 49-54

Sterling in combination with Powell, Fromming and Fennell

Claim 33 defines a pharmaceutical composition comprising a first intraoral portion and a second oral portion containing a pharmaceutically active ingredient which is released into the intestine after the intraoral portion has disintegrated. Claim 33 requires the second portion be either a sustained release or a chewable formulation. None of the prior art teaches the desirability of a single formulation providing release at two sites and times: intraoral (first) and oral (second). None of the prior art discusses the problems with first pass metabolism. None of the prior art teaches the criteria for selecting a compound which can be absorbed intraorally. The claimed subject matter cannot be obvious unless one skilled in the art is led to combine drugs that can be combined so that one is released first, in the mouth, and absorbed there, followed by a second drug that can be ingested for subsequent absorption lower in the gastrointestinal tract. Many drugs, as discussed in the application, are not absorbed intraorally. It is well established that the mere possibility something may occur is not sufficient to make it obvious. The prior art must lead one to the claimed composition, with the motivation and enablement to make and use it as claimed, with a reasonable expectation of success.

Sterling does not disclose a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level, wherein the

active ingredient is as defined in claim 33. Sterling fails to disclose a second component which is either chewable or provides sustained release. Sustained release is where the drug is released over an extended period of time, for example 0.5 to 24 hours (page 23, lines 21-26). Delayed release as described by Sterling, is not the same as sustained release.

Fennell discloses a formulation containing miraculin and a non-toxic alkaline material. The composition can be powdered, liquid or formed into a tablet. The tablet is composed of a core comprising the active material and a non-toxic binder with the alkaline material forming a coating or being admixed in the core (Fennell, column 2, lines 54-62). There is no disclosure of a second drug. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. Fennell is not concerned with making a drug formulation wherein one portion is intraoral and the other portion is released for uptake in the stomach. Components in Fennell are released in the mouth, one neutralizing the mouth, the other coating the tongue. It is clear from the discussion in Fennell that the composition can be in any format, not necessarily a tablet. There would therefore no motivation for a skilled artisan to combine Fennell with Sterling. The mere fact that Fennell discloses that the tablet can be coated with the alkaline material as a film or compressed thereon, does not provide one of ordinary skill in the art with a reason to combine Fennell with Sterling. The Examiner has stated no objective reason why one of ordinary skill in the art would combine Fennell and Sterling. The same is equally applicable with respect to Frömming and Powell, which disclose compounds that may be incorporated into the claimed composition, but no teaching leading one skilled in the art to make the composition. The only way one can arrive at the claimed composition is using the hindsight of appellants' disclosure.

Neuser in combination with Lewis and Liedtke

The references do not disclose each and every element of the claims. The claimed compositions contain a first intraoral and a second oral active agent, wherein the second portion is either a sustained release or chewable formulation. Lewis and Liedtke do not provide the elements missing from Neuser. A combination of Lewis and Neuser as asserted by the Examiner would result in a formulation having as a fast acting component buprenorphine, and as a second component a systemically acting analgesic as listed in Neuser. Neuser requires the first portion be a locally acting analgesic with a rapid onset of action. Neuser further discloses that local anesthetics of this type display their action after less than one minute but have only a short duration of action (Neuser [0002]). Buprenorphine is a long acting drug. One of ordinary skill in the art would therefore not have motivated to substitute Neuser's anesthetics with buprenorphine as asserted by the Examiner. Even if one of ordinary skill in the art did make such a substitution combining Neuser and Lewis, one would not arrive at the claimed composition. Further, one of ordinary skill in the art would not be motivated to combine the references as Liedtke discloses **topical** formulations, not oral formulations as defined in the claims. Accordingly, claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are not obvious over Neuser in view of Lewis and Liedtke.

Claims 33-43 and 49-57 are not obvious over Barclay in view of Pather.

The claimed compositions contain an intraoral portion which rapidly dissolves and is therefore released rapidly after coming in contact with the patient's saliva for immediate absorption in the mouth; preferably within ten minutes. The active agent in the oral portion is released due to dissolution of the carrier or degradation of the sustained release matrix. It is not released by being pushed out a passageway drilled through the core as described in Barclay. The

main objective is to overcome the problems encountered in buccal delivery of drugs, by making a device for buccal delivery of drugs for an extended period of time (see Barclay, column 4). This actually is teaching away from the presently claimed formulation which requires that the intraoral portion be rapidly released. One of ordinary skill in the art would not be motivated to combine Barclay and Panther to arrive at the claimed compositions. Barclay described devices where the drug is release by being pushed put a passageway, which is drilled into the core of the device. Panther describes effervescent agents act to increase the rate and extent of absorption. Accordingly, claims 33-43 and 49-57 are not obvious over Barclay in view of Panther.

Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious over Johnson.

The claimed compositions contain an **intraoral** portion that rapidly dissolves or disintegrates immediately upon administration and is immediately absorbed. Johnson does not disclose a second oral formulation that is in a sustained release or delayed release formulation. The claimed compositions are designed to be swallowed once the intraoral layer has disintegrated. Chewing gum is not normally swallowed. Johnson does not disclose the composition of claim 33 in the form of a capsule or tablet (claims 35-36 and 38-39). Johnson does not recite each and every claim limitation, and therefore cannot make obvious the claims. Accordingly, claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious in view of Johnson.

The Prior Art does not disclose each element of the claims

None of the prior art discloses or teaches that the outer portion of the composition must dissolve or disintegrate rapidly to release only the intraoral portion, nor indeed why this would necessary or advantageous. Fennell discloses a film coating but that alone does not mean that it would dissolve or disintegrate rapidly. Indeed, many film coatings are enteric coatings

especially designed not to release until after passage through the stomach. Sterling does not disclose a composition wherein an intraoral portion is film coated or coated with a compression coating. Sterling describes compositions wherein the intraoral portion is dusted onto the core. Nether Powell, Fromming, nor Fennell make up for this deficiency.

None of the prior art teach the claimed dosage range for the intraoral component, which is important since larger dosages are unlikely to be absorbed intraorally, as well as the physical limitations on how much of a drug can be incorporated around the core of a second drug which is to be released orally. This is also not obvious from any of the art, because there is no disclosure of intraoral delivery other than possibly Frömming, but as noted above this is not clear.

None of the prior art teaches that there must be a second component which is orally delivered in a sustained release or chewable formulation. The prior art teaches chewable formulations, but we do not know if this is for intraoral or oral delivery, nor that the drug as described is in a dosage and form suitable for intraoral delivery. Sterling does not teach a chewable formulation. The Examiner has provided no technical reasoning for his assertion that Sterling reads on the chewable formulation as claimed by Appellants. While it might be true that the core in Sterling can be chewed, this does not mean that it is intended to be chewed, nor that it must be a product that is absorbed in the lower gastrointestinal tract. The way a drug product is designed and manufactured affects the bioavailability of the drug. For example, different drug products that contain the same active ingredient may have different bioavailability depending on differences in the inactive ingredients even if they are administered in the same way (for example as a swallowable tablet). The rate of dissolution of a solid drug form may also affect absorption. The consistency of a tablet meant to be chewed is different from that of a tablet meant to be swallowed whole, and chewing increases surface area and rate of dissolution of the

drug (please see Johnson, page 2, line 22, until page 3, line 19). Furthermore, a tablet that is intended to be chewed would include sweetening and flavoring agents which help to improve patient compliance, something that would not be of concern to the manufacturer, if the drug were intended to be swallowed whole. Therefore, a drug formulation that is intended to be swallowed does not inherently disclose a chewable formulation because they have very different characteristics.

In summary, none of the prior art discloses the general concept of a two component formulation for initial intraoral delivery followed by oral delivery; a rapidly disintegrating or dissolving coating over an intraoral drug, the selection of a drug for intraoral delivery in a dosage range of between 1 and 50 mg, nor the combination with a sustained release or chewable second component for oral delivery. Absent motivation to combine as appellants have done, the claimed composition would not be obvious from the cited art.

Claim 34

None of the cited art discloses or leads one to select the intraoral component of a two component system as one which would otherwise undergo first pass metabolism.

Claim 37

None of the cited art discloses multilayer tables with multiple layers of an intraoral and/or oral component.

Claims 41 and 50

Claim 41 differs from claim 33 by requiring that the drug to be delivered intraorally is either as listed in claim 33 or has a molecular weight not exceeding 350 daltons, and requires either an effervescence or pharamaceutically acceptable signaling system between the two components.

Claims 41 and-56 are not obvious over Sterling in view Powell, and further in view of Frömming or Fennell.

Sterling does not disclose a pharmaceutical composition with an active ingredient having a molecular weight not exceeding 350 daltons, or an active ingredient selected from the ingredients listed in claim 41. Sterling does not disclose a pharmaceutical composition comprising a pharmaceutically acceptable effervescent agent which generates effervescence or a pharmaceutically acceptable signaling system, located between the first intraoral component and the second oral component, which is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid as defined by claim 41. Sterling also does not disclose a composition wherein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core. Neither Powell, Fromming, nor Fennell make up for this deficiency.

None of the prior art discloses the general concept of a two component formulation for initial intraoral delivery followed by oral delivery; a rapidly disintegrating or dissolving coating over an intraoral drug, the selection of a drug for intraoral delivery in a dosage range of between 1 and 50 mg, nor the combination with a sustained release or chewable second component for oral delivery. None of the art discloses placing an effervescent agent in the intraoral component. None of the art discloses placing a signaling means between the intraoral and oral components. Thus, there would is no motivation to combine or modify as required to arrive at the claimed compositions.

Claims 43 and 44

Claim 43 requires the second oral component to be a sustained release formulation; claim 44 requires sustained release over a period of 0.5 to 24 hours.

None of the cited art discloses a second component in a two component formulation which provides sustained release as required by claims 43 and 44. Sustained release is defined as where the drug is released over an extended period of time, for example 0.5 to 24 hours (page 23, lines 21-26). Delayed release which is taught by Sterling, is not the same as sustained release. None teach sustained release except in the case of an osmotic device, which is not part of a two component system where there is a first intraoral component, nor any teaching that would lead one to combine two such component.

Claims 45 and 46

None of the cited art discloses a two component system wherein the second component is for oral delivery and provides for delayed release. There is no motivation to modify and combine any of the cited art as appellants have done to create a single formulation that can deliver drug immediately intraorally, then release much later a second component after passage through the stomach.

Claim 47

None of the cited art discloses a pharmaceutical composition with two portions wherein the second portion is chewable, and comprises at least one pharmaceutically acceptable excipient suitable for a chewable medication and a flavoring agent, nor any motivation to make such a combination.

Claim 48

Claim 48 requires the first intraoral component to disintegrate or dissolve within 10 minutes, when the composition is contacted with saliva during intraoral administration. Claim 49 requires the second oral component to remain intact until the intraoral administration of the first intraoral component has been delivered.

The examiner has cited no art teaching the criticality of a two component system wherein the first component dissolves or disintegrates within 10 minutes, nor where the second component must remain intact after the first component is delivered. Indeed, these features are integral to a two component delivery system releasing drug at different places and different times, and is simply not discloses by nor obvious from any aspect of the cited prior art. The examiner has done nothing more than generally group all claims together and ignore the features that make this such a desirable system for those individuals in need of combined drug therapy, where an initial very rapid onset is essential, followed later by delivery of drug orally.

Claim 53

The examiner has cited no art disclosing the claimed dosage range of one to 50 mg, much less the claimed range of 10 to 30 mg of claim 53, for a drug to be delivered intraorally. The prior art fails to recognize the desirability or reason one would deliver initially a first component intraorally, that requires drugs that chemically can be absorbed intraorally, as well as a dosage that can be absorbed intraorally. The prior art is completely silent on either of these important claim limitations.

Claims 55-57

Claims 55-57 define a process for making the formulation of claim 33.

The same arguments made with respect to the formulations are equally applicable here. Sterling does not disclose a process for preparing a pharmaceutical composition in unit dosage, comprising two portions wherein the first is an intraoral portion which disintegrates to release a pharmaceutically effective amount of at least one active ingredient which is absorbed intraorally due to the chemical composition and dosage and a second portion which is released and absorbed within the lower gastrointestinal tract from either a sustained release or chewable formulation.

Claims 41, 51, and 54 are not obvious over Sterling in view of Remington and Fennell.

Claims 41, 51 and 54, Sterling and Fennell, are discussed above.

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, this having an outer medicinal layer soluble in the mouth. Sterling does not disclose a pharmaceutical composition comprising a pharmaceutically acceptable effervescent agent which generates effervescence or a pharmaceutically acceptable signaling system, located between a first intraoral component and a second oral component, which is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid. Sterling also does not disclose a composition where the intraoral portion is a film coating applied to the core or a compression coating compressed around the core.

Remington states that nitroglycerin has a molecular weight of 227.09 and that the dose of nitroglycerin is between 1 mg and 0.15-0.6 mg for buccal tablets and sublingual tablets, respectively.

Fennell describes a composition for rendering sour tasting foods sweet tasting comprising miraculin glycoprotein obtained from the ripe fruit of *Synsepalum dulcificum* and a non-toxic alkaline material. The composition is placed in the mouth 1-2 hours before ingesting sour food.

Remington and Fennell do not disclose the claim elements missing from Sterling. One of ordinary skill in the art would not be motivated to combine Sterling and Remington and/or Fennell to make a two component system, much less one containing either an effervescent material in an outer coating or a signaling system between the two components, nor would one achieve the claimed composition even if the prior art were combined. Fennell describes a taste masking composition which is ingested before ingesting sour-tasting foods. The taste masking

composition neutralizes mouth acids and coats the tongue. Fennell does not disclose or suggest coating a composition containing an intraoral component and an oral component as defined in claims 41, 51, and 54. Therefore, Claims 41, 51, and 54 are not obvious over Sterling in view of Remington and Fennell.

Claim 57 is not obvious over Johnson in view of Jao.

Claim 57 depends from claim 55 which defines a process for the preparation of a composition containing a first intraoral portion and a second oral portion, wherein the second oral component is a tablet core or at least one layer of a multi-layer tablet or an uncoated capsule. Johns describes chewing gums, not capsules or tablets. Jao describes a dosage form containing a wall that surrounds a lumen comprising the drug, a driving means for delivering the drug, and a rate controlled exit means. One of ordinary skilled in the art would not be motivated to combine the chewing gums of Johnson with the dosage form described in Jao. The references, in combination, do not disclose each and every element of claim 57 nor the motivation to combine.

(d) Double Patenting Rejection

Claims 33-57 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,863,901 and claims 1-20 copending U.S.S.N.. 11/041,474. In response, Appellants will file a terminal disclaimer to overcome the double patenting rejection upon indication that the claims are otherwise allowable and assuming that the rejection is maintained in view of the status of the claims in U.S.S.N. 11/041,474 at the conclusion of the appeal.

(e) Conclusion

For the foregoing reasons, Appellants submit that claims 1-57 are definite under 35 U.S.C. 112, and non-obvious over the cited art, alone or in combination. The prior art fails to

disclose the elements of, and the motivation to combine, as appellants have done, with a reasonable expectation of success, a formulation that provides in a single convenient and economical formulation:

A first component that is rapidly released in the mouth, where the drug is in a dosage (one to 50 mg or 10 to 30 mg) and is chemically able to be rapidly absorbed intraorally, and

A second component that is released and absorbed in the lower gastrointestinal tract following oral administration, which can be in a sustained or delayed release formulation,

Which can include within the first component effervescence agents to increase rate of dissolution and uptake of drug, or a signaling mechanism to tell the individual the first dose has been delivered and the second component can now be swallowed.

Respectfully submitted,

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(8) Claims Appendix: Claims On Appeal

33. A pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is capable of sublingual or buccal absorption through the mucous membranes of the mouth in a therapeutically effective level,

wherein the active ingredient is selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration, wherein the intraoral portion is a film coating that is applied to the core or a compression coating that is compressed around the core; and

(b) a second oral portion located within the first portion which contains a pharmaceutically active ingredient, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

34. The pharmaceutical composition of claim 33 wherein the active ingredient would otherwise undergo first pass metabolism.

35. The pharmaceutical composition of claim 33 in a tablet or capsule unit dosage form.

36. The pharmaceutical composition of claim 35 wherein the unit dosage form is a tablet and the second oral portion of the composition is an inner core of the tablet surrounded by an outer coating of the first intraoral component.

37. The pharmaceutical composition of claim 35 wherein the unit dosage form is a multi-layer tablet wherein the second oral portion of the composition comprises one or more inner layers of the tablet and the first intraoral component comprises one or more of the outer layers of the multi-layer tablet.

38. The pharmaceutical composition of claim 36 wherein the outer coating is a film coat that is applied as a layer to the inner core.

39. The pharmaceutical composition of claim 36 wherein the outer coating is a compression coat that is compressed around the inner core.

40. The pharmaceutical composition of claim 33 comprising an outer film coating comprising at least one pharmaceutically acceptable coating polymer selected from the group consisting of cellulose, hydroxypropyl methylcellulose, methyl cellulose, polyvinylpyrrolidone, and polyethylene glycol, a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable glidant and a pharmaceutically acceptable colorant.

41. A pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient for uptake in the oral cavity in a therapeutically effective level,

the active ingredient having a molecular weight not exceeding 350 daltons or an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine,

Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration, wherein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core;

(b) a pharmaceutically acceptable effervescent agent which generates effervescence or a pharmaceutically acceptable signaling system, located between the first intraoral component and the second oral component, that is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid; and

(c) a second oral portion located within the first portion which contains a pharmaceutically active agent, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved.

42. The pharmaceutical composition of claim 33 comprising a pharmaceutically acceptable flavoring agent in the first intraoral component.

43. The pharmaceutical composition of claim 33 wherein the second oral component is in a sustained release formulation.

44. The pharmaceutical composition of claim 43 wherein the sustained release is over a period of 0.5 to 24 hours.

45. The pharmaceutical composition of claim 33 comprising a delayed release coating.

46. The pharmaceutical composition of claim 45 wherein release is delayed for a period of 0.5 to 12 hours.

47. The pharmaceutical composition of claim 33 wherein the second oral component is chewable and comprises at least one pharmaceutically acceptable excipient suitable for a chewable medication and a flavoring agent.

48. The pharmaceutical composition of claim 33 wherein the first intraoral component disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva during intraoral administration.

49. The pharmaceutical composition of claim 33 wherein the second oral component remains intact until the intraoral administration of the first intraoral component has been delivered.

50. The pharmaceutical composition of claim 33 further comprising a pharmaceutically acceptable signaling system located between the first intraoral component and the second oral component that is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component.

51. The pharmaceutical composition of claim 41 where in the pharmaceutically active ingredient in the first intraoral component having a molecular weight not exceeding 350 Daltons is selected from the group consisting of analgesics, antihistamines, antidiarrheals, anxiolytics, hypnotics, stimulants, cardiovascular drugs, pulmonary drugs, anti-hypertensives, anti-emetics, anti-inflammatory drugs, renal drugs, steroids, drugs for neurological disorders, anti-psychotic drugs, drugs for treating endocrine disorders, drugs for promoting immune response, drugs for treating osteoarthritis, drugs for treating glaucoma, drugs for treating allergic rhinitis, drugs for treating anemias and other hematological disorders, drugs for treating infectious diseases, drugs for the treatment and symptoms of cancer, drugs for insomnia, and antidiabetic drugs.

52. The pharmaceutical composition of claim 33 wherein the active ingredient in the first intraoral composition has a lower bioavailability upon oral administration when compared to intravenous administration.

53. The pharmaceutical composition of claim 33 wherein the active ingredient in the first intraoral composition is in a dosage of between 10 micrograms and 30 mg.

54. The pharmaceutical composition of claim 41 wherein the active ingredient has a molecular weight of less than 350 Daltons.

55. A process for the preparation of a pharmaceutical composition in unit dosage comprising

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is capable of sublingual or buccal absorption through the mucous membranes of the mouth in a therapeutically effective level,

wherein the active ingredient is selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration; and

(b) a second oral portion located within the first portion which contains a pharmaceutically active ingredient which is released for uptake into the intestine after the first

intraoral portion has disintegrated or dissolved in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved which comprises the steps of:

(i) providing the second oral component as an inner tablet core or as at least one layer of a multi-layer tablet core or as an uncoated capsule, wherein the second oral component is either a sustained release or chewable formulation; and

(ii) applying the first intraoral component as an outer layer or as several outer layers forming an outer coating on the first portion, wherein the intraoral component is a film coating applied to the core or a compression coating compressed around the core.

56. The process of claim 55 wherein the active ingredient exhibits first pass metabolism.

57. The process of claim 55 wherein the active ingredient has a molecular weight of less than 350 daltons.

(9) Evidence Appendix

No evidence has been submitted by the Appellants

(10) Related Proceedings Appendix

None